

## II. SPECIFICATION

Delete present page 3 and add the following in its place:

there is variation in *inter alia* the binding properties, for instance 1) of enzymes and proteins that play a role in fibrinolysis, or 2) binding of factor XIII, which influences the stability of the fibrin, or 3) variation in rate and extent of lateral growth of the fibrin, resulting in fibrin having e.g. thinner fibers, more branches, and the like.

One of the known variants is  $\gamma'$  (gamma') which is formed through alternative processing of the primary mRNA transcript. About 8% of the total  $\gamma$ -chains is of this form. The  $\gamma'$  chain consists of 427 amino acids and the four C-terminal amino acids (AGDV) have been replaced therein with an anionic sequence of 20-amino acids that contains 2 sulphated tyrosines. The fibrinogen  $\gamma'$  chain binds plasma factor XIII, but does not bind to the platelet fibrinogen receptor II $b\beta_3$ , this in contrast to the normal  $\gamma$  chain whose C-terminal sequence (400-411) plays a critical role in regulating platelet aggregation.

Another variant of fibrinogen is Fib420, which has a molecular weight of 420 kDa. In healthy persons, only traces are found but in exceptional cases, this variant accounts for as much as 5% of the total circulating fibrinogen. Through alternative splicing of the  $\alpha$ -chain transcript an extra open reading frame is included, so that an  $\alpha\alpha$ -chain arises which is extended on the carboxyterminal side by circa 35% (847 amino acids). The additional length of  $\alpha\alpha$ -chain has a nodular structure and as far as known, no fibrinogen molecules occur that have this additional piece on just one  $\alpha\alpha$ -chain. This fibrinogen variant Fib420 might be less sensitive to degradation and could have an effect on the clot structure.

Another cause of molecular heterogeneity in the fibrinogen molecules is a partial degradation of the carboxyterminal part of the  $\alpha\alpha$ -chain, which results in three forms of fibrinogen having a different molecular weight. Fibrinogen is synthesized in the high-molecular weight form